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# Hyperuricemia increases the risk of cardiovascular mortality associated with very high HdL-cholesterol level

Paolo Palatini [a,*], Agostino Virdis [c], Stefano Masi [c], Alessandro Mengozzi [c], Edoardo Casiglia [m], Valerie Tikhonoff [m], Arrigo F.G. Cicero [e], Andrea Ungar [g], Gianfranco Parati [b], Giulia Rivasi [d,g], Massimo Salvetti [f], Carlo M. Barbagallo [n], Michele Bombelli [k], Raffaella Dell'Oro [k], Berardino Bruno [i], Luciano Lippa [j], Lanfranco D'Elia [l], Maria Masulli [l], Paolo Verdecchia [o], Gianpaolo Reboldi [g], Fabio Angeli [p,z], Francesca Mallamaci [q], Massimo Cirillo [r], Marcello Rattazzi [s], Pietro Cirillo [t], Loreto Gesualdo [t], Alberto Mazza [u], Cristina Giannattasio [v], Alessandro Maloberti [v], Massimo Volpe [w,aa], Giuliano Tocci [w,aa], Guido Iaccarino [x], Pietro Nazzaro [y], Ferruccio Galletti [l], Claudio Ferri [i], Giovambattista Desideri [i], Francesca Viazzi [h], Roberto Pontremoli [h], Maria Lorenza Muiesan [f], Guido Grassi [k], Claudio Borghi [e], from the Working Group on Uric Acid and Cardiovascular Risk of the Italian Society of Hypertension (SIIA)

[a] *Department of Medicine, Studium Patavinum, University of Padova, Padua, Italy*
[b] *IRCCS, Istituto Auxologico Italiano, Department of Cardiology, San Luca Hospital, Milan, Italy*
[c] *Department of Clinical and Experimental Medicine, University of Pisa, Italy*
[d] *Department of Medical and Surgical Science, University of Perugia, Perugia, Italy*
[e] *Alma Mater Studiorum University of Bologna, Bologna, Italy*
[f] *Department of Clinical and Experimental Sciences, University of Brescia, Italy*
[g] *Department of Geriatric and Intensive Care Medicine, Careggi Hospital and University of Florence, Italy*
[h] *Department of Internal Medicine, University of Genoa and Policlinico San Martino, Genova, Italy*
[i] *Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy*
[j] *Italian Society of General Medicine (SIMG), Avezzano, L'Aquila, Italy*
[k] *Department of Cardiovascular, Neural and Metabolic Sciences, Clinica Medica, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy*
[l] *Department of Clinical Medicine and Surgery, "Federico II" University of Naples Medical School, Naples, Italy*
[m] *Department of Medicine, University of Padua, Padua, Italy*
[n] *Biomedical Department of Internal Medicine and Specialistics, University of Palermo, Palermo, Italy*
[o] *Hospital S. Maria della Misericordia, Perugia, Italy*
[p] *Department of Medicine and Surgery, University of Insubria, Varese, Italy*
[q] *CNR-IFC, Clinical Epidemiology of Renal Diseases and Hypertension, Reggio Cal Unit, Reggio Calabria, Italy*
[r] *Department of Public Health, "Federico II" University of Naples, Napoli, Italy*
[s] *Department of Medicine - DIMED, University of Padova, Medicina Interna 1, Ca' Foncello University Hospital, Treviso, Italy*
[t] *Department of Emergency and Organ Transplantation - Nephrology, Dialysis and Transplantation Unit, Aldo Moro University of Bari, Bari, Italy*
[u] *Department of Internal Medicine, Hypertension Unit, General Hospital, Rovigo, Italy*
[v] *Cardiology IV, 'A. De Gasperis' Department, Niguarda Ca' Granda Hospital, Health Science Department, Milano-Bicocca University, Milano, Italy*
[w] *Hypertension Unit, Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University of Rome Sapienza, Sant'Andrea Hospital, Rome, Italy*
[x] *Department of Advanced Biomedical Sciences, "Federico II" University of Naples, Napoli, Italy*
[y] *Department of Medical Basic Sciences, Neurosciences and Sense Organs, University of Bari Medical School, Bari, Italy*
[z] *Department of Medicine and Cardiopulmonary Rehabilitation. Maugeri Care and Research Institutes, IRCCS Tradate, Varese, Italy*
[aa] *IRCCS Neuromed, Pozzilli (IS), Italy*

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* Corresponding author. Studium Patavinum, University of Padova, Padua, Italy, Via S. Fris 121, 31029 Vittorio Veneto, Italy
*E-mail address:* palatini@unipd.it (P. Palatini).

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**KEYWORDS**
HDL-Cholesterol;
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**Abstract** *Background and aims:* Whether the association between very high HDL-cholesterol levels and cardiovascular mortality (CVM) is modulated by some facilitating factors is unclear. Aim of the study was to investigate whether the risk of CVM associated with very high HDL-cholesterol is increased in subjects with hyperuricemia.
*Methods and results:* Multivariable Cox analyses were made in 18,072 participants from the multicentre URRAH study stratified by sex and HDL-cholesterol category. During a median follow-up of 11.4 years there were 1307 cases of CVM. In multivariable Cox models a J-shaped association was found in the whole population, with the highest risk being present in the high HDL-cholesterol group [>80 mg/dL, adjusted hazard ratio (HR), 1.28; 95%CI, 1.02−1.61; p = 0.031)]. However, a sex-specific analysis revealed that this association was present only in women (HR, 1.34; 95%CI, 1.02−1.77; p = 0.034) but not in men. The risk of CVM related to high HDL-cholesterol was much greater in the women with high uric acid (>0.30 mmol/L, HR 1.61; 95% CI, 1.08−2.39) than in those with low uric acid (HR, 1.17; 95%CI, 0.80−1.72, p for interaction = 0.016). In women older than 70 years with hyperuricemia the risk related to high HDL-cholesterol was 1.83 (95%CI, 1.19−2.80, p < 0.005). Inclusion of BMI in the models weakened the strength of the associations.
*Conclusion:* Our data indicate that very high HDL-cholesterol levels in women are associated with CVM in a J-shaped fashion. The risk of CVM is increased by concomitant hyperuricemia suggesting that a proinflammatory/oxidative state can enhance the detrimental cardiovascular effects associated with high HDL-cholesterol.


## 1. Introduction

High-density lipoprotein cholesterol (HDL-C) is a blood lipid component that has been considered to be beneficial to cardiovascular health and its routine measurement is currently recommended by all international guidelines. This concept is based on the results of a large number of early epidemiological studies that showed an inverse linear association between HDL-C concentration and risk of cardiovascular disease [1−3]. However, early studies did not focus on the predictive value of very high levels of HDL-C.

Recent investigations have suggested a more complicated relationship between HDL- C and cardiovascular events showing that extremely high HDL-C levels may paradoxically be associated with adverse cardiovascular outcomes. Indeed, a U-shaped or even J-shaped association between HDL-C and cardiovascular events or mortality has been observed in several general population studies [4−6] as well as in diabetic [7], hypertensive [8] and coronary [9] patients. However, inconclusive results have been reported for cardiovascular mortality (CVM) which showed an association with high HDL-C in some studies [9,10] but not in other reports [4,11−14]. In addition, in several negative studies no sex-specific data were provided [12,13]. Another poorly explored aspect is whether the putative association between high HDL-C and CVM may be influenced by some facilitating factors. In the NHANES study a greater risk of mortality and higher level of inflammatory factors were found in the subjects with extremely high HDL-C suggesting that in this group a high level of oxidative stress may have influenced the HDL-C-CVM association [15].

Uric acid is a heterocyclic organic compound and an end product of purine metabolism in humans [16]. Uric acid acts as a pro-oxidant and pro-inflammatory factor at high concentration [16,17], and thus might aggravate the risk of CVM associated with high HDL-C. It is thus possible that the adverse cardiovascular effects of high HDL-C are more pronounced in subjects with hyperuricemia as suggested by previous research [18]. This hypothesis was explored in the Uric acid Right for the heArt Health (URRAH) project, a multicentre study designed by the Working Group on uric acid and cardiovascular risk of the Italian Society of Hypertension [19,20]. The purpose of the present analysis was to verify whether high HDL-C [(>2.07 mmol/L (>80 mg/dL)] is associated with CVM in sex-specific analyses and whether this risk is increased in subjects with hyperuricemia by leveraging data from the URRAH study.

## 2. Methods

### 2.1. Population

The URRAH project is an Italian multicentre retrospective, observational study [19,20]. Aim of the URRAH is to study the relationship between uric acid and cardiovascular disease within a large sample of normotensive and hypertensive subjects. The database was constructed by merging data from several cohorts recruited within the Italian Centres of Hypertension and distributed in almost all the Italian regions. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Subjects recruited in prospective observational cohort studies as well as patients attending hypertension clinics were included. Patients with previous cardiovascular

events were excluded. For the present study, we selected 18,072 participants (9509 women) in whom fasting HDL-C, low-density lipoprotein (LDL)-cholesterol, triglyceride, uric acid, creatinine, office blood pressure (BP), and information on cardiovascular risk factors and fatal cardiovascular events during the follow-up were available.

The study protocol was approved by the local Ethics Committees in all participating Centres and written informed consent was obtained from all of the participants.

### 2.2. Procedures

Biochemical tests were measured using standard methods. Diabetes mellitus was defined by treatment with antidiabetic drugs, fasting plasma glucose ≥6.99 mmol/L (126 mg/dL), or haemoglobin A1c ≥ 48 mmol/mol (≥6.5%). LDL-cholesterol was calculated as: total cholesterol minus HDL-C levels, minus triglyceride level divided by 5, if the triglyceride level was less than 400 mg/dL. Lipid lowering drugs were taken by 8.0% of the participants. Mortality from major cardiovascular diseases (International Classification of Diseases, Tenth Revision (ICD-10) included fatal events due to acute myocardial infarction, heart failure or stroke and sudden cardiac death. Information about death was obtained from hospital records or death certificates. Other details of the URRAH project and the procedures used to measure covariates have been previously published [19,20].

### 2.3. HDL-cholesterol categories

Four categories of HDL-C were identified: less than 1.035 mmol/L (40 mg/dL), 1.035–1.55 mmol/L (40–60 mg/dL), 1.55–2.07 mmol/L (60–80 mg/dL), and more than 2.07 mmol/L. In agreement with previous investigations, people with HDL-C >2.07 mmol/L (>80 mg/dL) were defined as having high HDL-C [8,9,13]. In the survival analyses, the 1.035–1.55 mmol/L group was used as the reference category [4,9].

### 2.4. Statistics

Statistical analysis was carried out using SYSTAT version 12 (SPSS Inc., Chicago, IL, USA) and Medcalc version 20.014 (Ostend, Belgium) packages. Differences in mean values were tested with an unpaired Student *t*-test. Comparisons between the four HDL-C female categories were carried out using an analysis of covariance adjusting for age. The Chi-squared test was used to evaluate differences between categorical variables. The associations between HDL-C category and time to CVM were analyzed in the participants stratified by sex using the Cox proportional hazards regression model. All models were initially adjusted for age. Subsequently, all models were further adjusted for the following variables: smoking, diabetes mellitus, systolic BP, serum LDL-cholesterol, triglyceride (log-transformed), uric acid, and creatinine. Further adjustment was made for BMI. For all analyses, the follow-up time was defined as the period between the baseline visit and the last confirmed follow-up or date of event. We used a Wald test for the regression coefficients to test the null hypothesis that risk factors had no effect. The hazard ratios (HR) from the multivariable analyses and their corresponding two-sided 95% confidence intervals (CI) were derived from the regression coefficients in the Cox models. We tested for the presence of a nonlinear effect of HDL-C level on CVM by adding a squared term to the models. The joint effect of HDL-C group and uric acid on CVM was also analyzed using uric acid as a categorical variable to facilitate interpretation and risk stratification in clinical practice. To identify a meaningful cut-point value for uric acid in women, the receiver operating characteristic (ROC) curves method was used according to De Long et al. [21]. The Youden's index was used as a criterion for selecting the optimum cut-point. The area under the curve was also provided (Supplementary Table S1). To examine whether there was an interactive effect of HDL-C with other clinical variables on CVM, a series of sensitivity analyses were performed in subjects ≤70 years or >70 years, smokers versus non smokers, normotensives versus hypertensives, diabetics versus non diabetics, and subjects with BMI ≤25 kg/m$^2$ versus >25 kg/m$^2$. Analyses were performed using a significance level of $\alpha = 0.05$ (2-sided).

## 3. Results

Characteristics of the participants stratified by sex are reported in Table 1. Women were slightly heavier than men, were more frequently diabetic and less frequently smokers. Uric acid, creatinine, and triglyceride were lower in women than men, while HDL-C was higher in women. No between-sex difference was found for age, BP and LDL-cholesterol.

A significant inverse correlation was found between uric acid and HDL-C in the whole group ($-0.206$ $p < 0.001$) and in both genders. However, in the top HDL-C group no correlation was found between the two variables ($R = 0.013$, $P = 0.67$) in either gender.

**Table 1** Characteristics of the URRAH participants stratified by sex.

| N | Women | Men | p-value |
|---|---|---|---|
| | 9050 | 7978 | |
| Age, years | 58.8 (15.2) | 58.5 (14.5) | 0.19 |
| BMI, kg/m$^2$ | 26.8 (4.6) | 26.6 (4.2) | 0.005 |
| Office SBP, mmHg | 143.3 (24.8) | 143.1 (22.7) | 0.63 |
| Office DBP, mmHg | 84.4 (12.8) | 84.3 (12.3) | 0.59 |
| HDL-cholesterol, mmol/L | 1.41 (0.40) | 1.33 (0.38) | <0.001 |
| LDL-cholesterol, mmol/L | 3.48 (0.92) | 3.49 (0.95) | 0.65 |
| Triglyceride, mmol/L * | 1.21 (10.66) | 1.24 (9.56) | <0.001† |
| Uric acid, mmol/L | 0.29 (0.08) | 0.31 (0.08) | <0.001 |
| Creatinine, mmol/L | 0.080 (0.025) | 0.084 (0.019) | <0.001 |
| Hypertension, yes | 66.5% | 67.2% | 0.007 |
| Diabetes, yes | 10.7% | 9.5% | 0.012 |
| Smoking, yes‡ | 28.0% | 42.1% | <0.001 |

Data are mean (SD) or proportions. BMI indicates body mass index; SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein. *median (range); †p for log-transformed data; ‡smoker or ex-smoker.

**Table 2** Age-adjusted characteristics of the female participants stratified by HDL-cholesterol group.

| N | ≤1.035 mmol/L (≤40 mg/dL) | >1.035–1.55 mmol/L (>40–60 mg/dL) | >1.55–2.07 mmol/L (>60–80 mg/dL) | >2.07 mmol/L (>80 mg/dL) | p-value |
|---|---|---|---|---|---|
| | 1615 | 4594 | 2278 | 563 | |
| Age, years | 59.2 (0.4) | 58.1 (0.2) | 59.2 (0.3) | 61.9 (0.6) | <0.001 |
| BMI, kg/m$^2$ | 28.3 (0.1) | 27.1 (0.1) | 25.8 (0.1) | 24.4 (0.2) | <0.001 |
| SBP, mmHg | 145.6 (0.5) | 143.3 (0.3) | 141.6 (0.5) | 143.4 (0.9) | <0.001 |
| DBP, mmHg | 85.3 (0.3) | 84.3 (0.2) | 83.9 (0.3) | 85.2 (0.5) | 0.003 |
| HDL-Cholesterol, mmol/L | 0.90 (0.003) | 1.30 (0.003) | 1.77 (0.003) | 2.31 (0.006) | <0.001 |
| LDL-Cholesterol, mmol/L | 3.46 (0.02) | 3.56 (0.01) | 3.44 (0.02) | 3.10 (0.04) | <0.001 |
| Triglyceride, mmol/L | 1.64 (9.38) | 1.25 (10.6) | 1.01 (7.11) | 0.88 (3.01) | <0.001*† |
| Uric acid, mmol/L | 0.321 (0.001) | 0.286 (0.002) | 0.268 (0.002) | 0.262 (0.004) | <0.001 |
| Creatinine, mmol/L | 0.086 (0.001) | 0.081 (0.000) | 0.077 (0.001) | 0.073 (0.001) | <0.001 |
| Diabetes, yes | 16.6% | 10.2% | 8.2% | 8.0% | <0.001 |
| Smoking, yes‡ | 34.3% | 28.5% | 24.1% | 20.8% | <0.001 |
| Cardiovascular death rate | 8.9% | 6.7% | 8.0% | 11% | <0.001 |

Data are mean (SEM) or proportions. BMI indicates body mass index; SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; HDL indicates high-density lipoprotein; LDL indicates low-density lipoprotein. *median (range); †p for log-transformed data; ‡smoker or ex-smoker.

The age-adjusted characteristics of the women, divided according to HDL-C group are reported in Table 2. In general, a graded negative relationship was found between HDL-C and risk factor level. Women in the high HDL-C group were slightly older, had lower level of BMI, LDL-cholesterol, triglyceride, uric acid, and creatinine, and were less frequently diabetic or smokers than the rest of the population. CVM rate showed a U-shaped relationship with HDL-C level, the high HDL-C group having the highest mortality rate.

### *3.1. Association of HDL-cholesterol category with cardiovascular mortality*

During a median follow-up of 11.4 years (IQR, 5.8–13.2) there were 1307 cases (7.7%) of CVM in the whole population, 7.7% among both women and men. In the high HDL-C category, the rate of CVM was 11.0% among the 563 women and was 7.1% among the 308 men. In a multivariable Cox model including confounders and other risk factors, a J-shaped association was found in the whole population, with the highest risk being present in the high HDL-C group (HR, 1.28; 95%CI, 1.02–1.61; p = 0.031). However, a sex-specific analysis revealed that this association was present only in women but not in men (Fig. 1). Among the women, the highest risk was present in the high HDL-C group (HR, 1.34; 95%CI, 1.02–1.77; p = 0.034) (p-value for non-linearity 0.027). The strength of the association was weakened (HR, 1.26; 95%CI, 0.95–1.67; p = 0.10) when BMI was included in the multivariable model. Uric acid was also an independent predictor of CVM in women (p = 0.008).

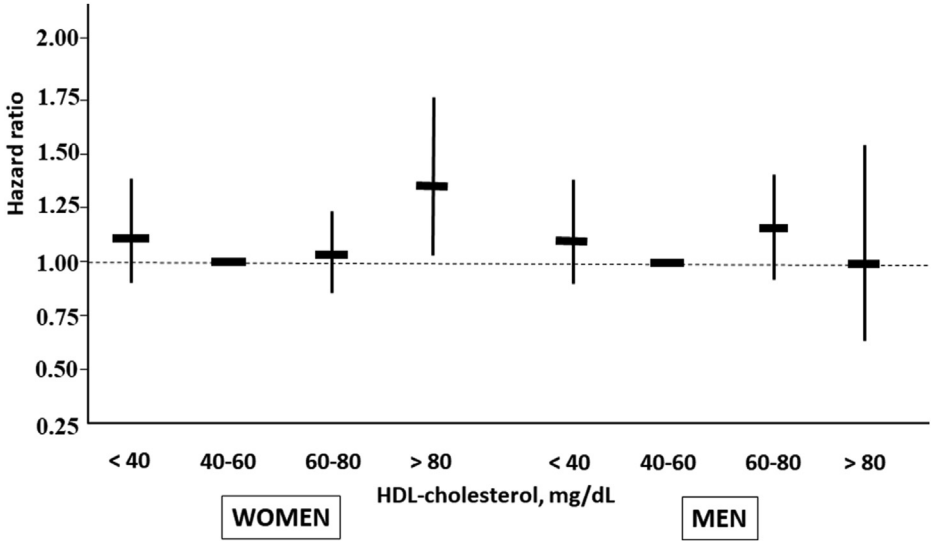


**Figure 1** Hazards ratios (95% confidence intervals) for cardiovascular mortality from multivariable Cox models in the HURRAH participants stratified by sex and HDL-cholesterol category. The 40-60 mg/dL category was used as reference. HDL indicates high-density lipoprotein.

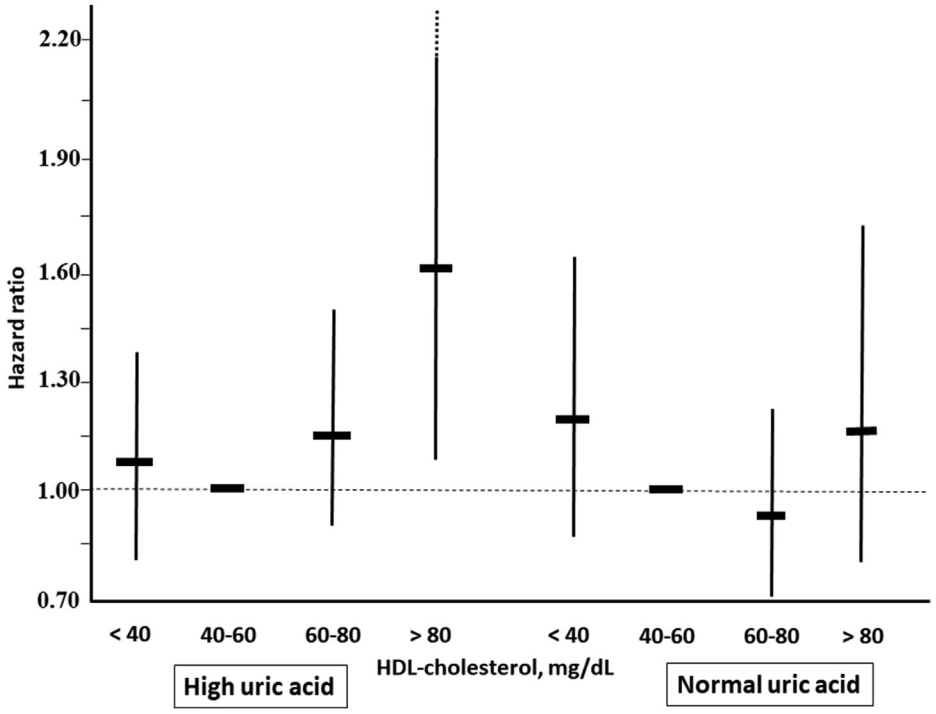


**Figure 2** Hazards ratios (95% confidence intervals) for cardiovascular mortality from multivariable Cox models in the female HURRAH participants stratified by uric acid level (≤0.30 versus >0.30 mmol/L) and HDL-cholesterol category. The 40-60 mg/dL category was used as reference. HDL indicates high-density lipoprotein.

### *3.2. Association of HDL-C and uric acid as categorical variables with CVM*

According to multivariable ROC analysis in women, optimal uric acid cut-off to discriminate between survivors and non survivors was 0.30 mmol/L (4.96 mg/dL) (Table S1). Hyperuricemia had a HR for CVM of 1.20 (95%CI, 1.02−1.41; p = 0.024).

In the main analysis, the female population was thus stratified according to HDL-C group and uric acid ≤0.30 mmol/L or >0.30 mmol/L. Among the women with hyperuricemia, again a J-shaped relationship was found between HDL-C and CVM. The HR associated with the high HDL-C group was 1.61 (95%CI, 1.08−2.39; p < 0.018) when uric acid level was >0.30 mmol/L (Fig. 2).

The HR was reduced to 1.51 (1.00−2.27, p = 0.049) when BMI was included in the model. In the setting of lower uric acid levels, a tendency to a U-shaped relationship was found but no HDL-C group showed an increased risk of CVM (Fig. 2). A significant interaction was found between high HDL-C and uric acid on CVM (Fig. 3).

### *3.3. HDL-cholesterol interaction with other variables*

In the whole female group, a significant interaction with high HDL-C category was found also for age (≤70 or >70 years) (Fig. 3). In the older women with hyperuricemia the risk of CVM associated with high HDL-cholesterol was 1.83 (1.19−2.80, p < 0.005) (Fig. 4). No interactive effect of high HDL-C on CVM was found for diabetes, smoking, BMI, and BP status.

## 4. Discussion

The results of this analysis obtained in a large sample of predominantly hypertensive patients show that there is a J-shaped relationship between HDL-C and CVM which in our study was confined to women. Both lowest and highest levels of HDL-C appeared to be associated with increased mortality risk but the association was significant only for the category with HDL-C >2.07 mmol/L. The novel finding of the present report is that the HDL-C-mediated risk of CVM was enhanced by concomitant hyperuricemia with a significant HDL-C-uric acid interaction on CVM. The higher risk found in the women with very high HDL-C can not be attributed to the concomitant adverse effect of traditional risk factors. In agreement with previous observations from the CANHEART study [14], women with high HDL-C had a less adverse cardiovascular risk profile than those in the lower HDL-C categories, in particular a lower prevalence of smokers and lower levels of LDL-cholesterol and triglyceride.

The measurement of HDL-C is currently used by clinicians to predict cardiovascular risk and the traditional belief is that higher HDL-C levels carry a better prognosis. This notion was mainly based on the results of early epidemiological studies which revealed an inverse association between HDL-C concentrations and risk of cardiovascular disease [1−3]. The lack of a curvilinear relationship between HDL-C and adverse outcomes found in those previous studies might be due to the limited number of subjects with very high HDL-C levels included in the analyses or to heterogeneity in the criteria used to identify HDL-C categories.

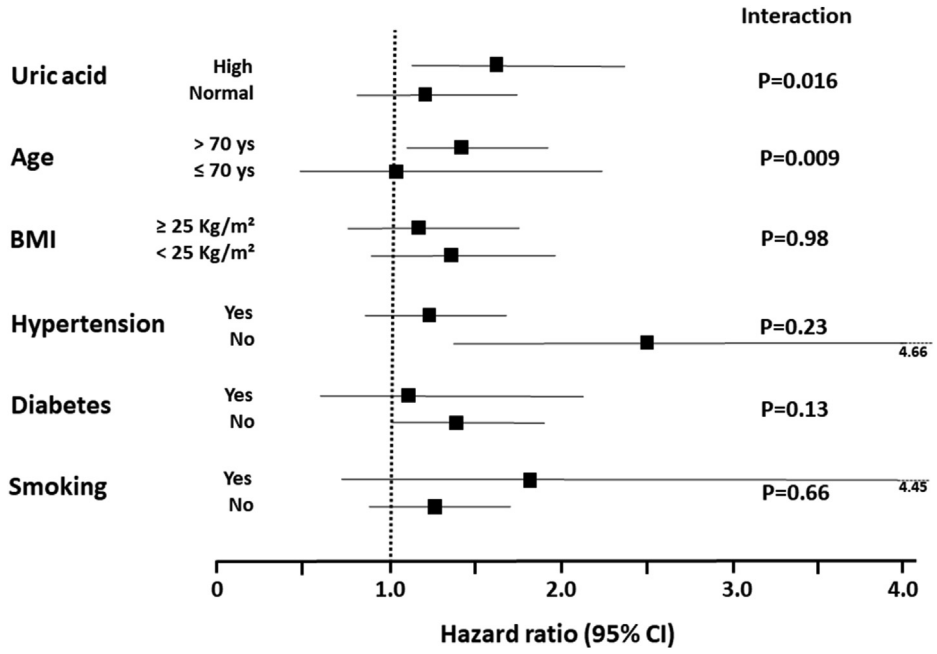


**Figure 3** Hazards ratios (95% confidence intervals) for cardiovascular mortality from multivariable Cox models (high HDL-cholesterol category versus reference category) in the female HURRAH participants stratified by covariates.

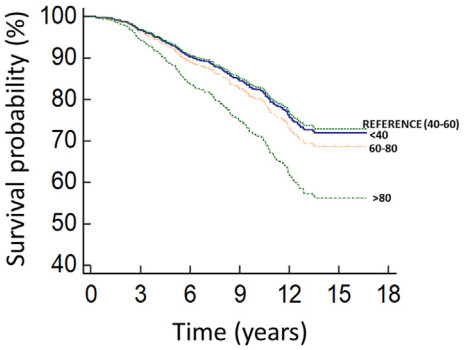


**Figure 4** Survival curves for risk of cardiovascular mortality by HDL-cholesterol category in the older (>70 years) female URRAH participants with uric acid > 0.30 mmol/L. Numbers refer to HDL-cholesterol level in mg/dL.

The present results are consistent with those of several recent studies and indicate that clinicians should not assume that high HDL-C is associated with a good prognosis. Recent research has shown that there is a non-linear relationship between HDL-C concentrations and CVM in general [10] or high risk populations [9]. A tendency to a J-shaped or U-shaped relationship was reported by several other investigators for a variety of adverse outcomes [6,22]. However, in many studies the association of high HDL-C with CVM did not reach the level of statistical significance [4,11–14]. These inconsistencies may be explained by demographic differences in sample groups across studies, or by the different presence and impact of other risk factors. In agreement with previous reports [15], in the present study inclusion of BMI in the survival models attenuated the strength of the relationship of HDL-C with adverse outcome.

### *4.1. Mechanisms for the HDL-C-CVM association and role of uric acid*

While the J-shaped relationship between high HDL-C and adverse cardiovascular outcomes seems to be a robust finding the mechanisms underlying this association remain unclear. HDL-C plays a key role in the pathways leading to atherosclerotic plaque formation, including reverse transportation of cholesterol, inflammatory/oxidative state, and regulation of vascular endothelial function [6,15,23]. A possible reason for the high HDL-C-adverse outcome association may be the complexity in composition and metabolism of HDL-C [24]. HDL-C particles are heterogeneous macromolecules, carrying many lipid species and proteins. According to some authors conformation and functionality of HDL may be altered in individuals with extremely high HDL-C levels [23,24], such that high HDL-C would favour rather than prevent cardiovascular disease. Another possible explanation for the increased CVM risk might be a dysfunction of HDL-C efflux capacity [12] which is considered a major anti-atherogenic property of HDL [25,26].

In this milieu, the risk of CVM associated with high HDL-C may be enhanced by some facilitating factors. A large wealth of studies including previous results from the URRAH project have shown that hyperuricemia is associated with several adverse outcomes including mortality from cardiovascular events [19,20,27]. At high concentration, uric acid acts as a pro-oxidant and pro-inflammatory factor [16,17,28]. Previous research has shown that the function of HDL-C particles can be converted from anti-inflammatory to pro-inflammatory under increased oxidative stress due to additional quantitative and qualitative molecular changes in HDL-C components [29]. In

1508 subjects from the cohort of the Turkish Adult Risk Factor Study, Onat et al. found that elevated levels of serum uric acid were associated with pro-inflammatory state and HDL dysfunction consistent with the hypothesis that uric acid mediates inflammation/oxidation enhancement and associated HDL dysfunction [18]. It is thus possible that the adverse cardiovascular effects of high HDL-C are more pronounced in subjects with hyperuricemia an effect that could be counteracted by appropriate uric acid lowering treatment. The increase in risk of uric acid and high HDL-C combined was not due to these variables being correlated to each other, because in the top HDL-C group no correlation was found in either gender.

An alternative explanation for the association of very high concentrations of HDL-C with CVM is that some individuals are carriers of genetic variants that cause an increase in circulating HDL cholesterol and promote concomitant detrimental effects that increase the risk of cardiovascular disease [30,31]. Finally, the association could simply be due to residual confounders such as alcohol intake which seemed to modify the relationship between HDL-C and mortality in some studies [32] but not in others [9,14], or the use of hormone replacement therapy in women [10].

In the present study, the increased cardiovascular risk associated with elevated levels of HDL-C in women was not confirmed in men. Conflicting data have been reported in the literature about the role of gender in the relationship between HDL-C and adverse outcome. In some studies a higher risk of CVM was found in women [10] while in some others the opposite was observed [9]. In some other studies no sex-specific analyses were carried out [12,13] often due to small sample sizes and thus evidence from the literature is inconclusive. This concern applies also to the present study because our dose–response analysis on HDL-C levels and CVM included only 308 men in the high HDL-C group and involved only 22 deaths, leading to less precise estimates compared with women.

### *4.2. Limitations*

The findings of the present study should be interpreted with caution considering the following limitations. As mentioned above, our study had limited power to detect the potential adverse effects of high HDL-C levels in men and thus the sex-related difference at high HDL-C levels needs to be validated by studies with a larger sample size. Another possible limitation is that the high HDL-C-CVM association may be caused by unrecognized or unmeasured confounders that can result in both high HDL-C levels and high CVM. Information on alcohol intake or use of hormone replacement therapy was missing in many URRAH participants and thus we could not investigate whether these factors were modulators of the HDL-C-CVM association. Finally, as our study was observational and retrospective no definitive conclusion about causality can be made.

## 5. Conclusions

Our data indicate that HDL-C level in women is associated with mortality from cardiovascular causes in a J-shaped dose–response pattern, with the highest risk observed at HDL-C levels higher than 2.07 mmol/L (80 mg/dL). Our observations have some implications for clinical practice challenging the conventional notion that higher levels of HDL-C are a protective factor. In addition, our findings indicate that the risk associated with high HDL-C is increased by concomitant hyperuricemia suggesting that a proinflammatory/oxidative state can enhance the detrimental cardiovascular effects of high HDL-C. These findings suggest that future mechanistic investigations need to address the HDL phenotype and function to better understand the role of HDL-C in cardiovascular disease risk. In individuals with extremely high HDL-C it seems warranted to recommend a careful evaluation aimed to reduce the impact of risk factors that may concur to determine cardiovascular disease. The intertwined relationship of hyperuricemia with high HDL-C found in the present study suggests that pharmacological reduction of uric acid to levels below 0.30 mmol/L (4.96 mg/dL) may decrease the CVM risk not only related to high uric acid but also to an abnormally high HDL-C level. Therefore, we advocate that future clinical research should investigate the prognostic impact of urate-lowering treatments in people with this metabolic association, with particular reference to women.

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## Declaration of competing interest

The authors declare that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.11.024.

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